*Send Orders for Reprints to reprints@benthamscience.net*

*Current Protein and Peptide Science,* 2014, *15,* 691-702



# Interactions Between Cholinergic and Fibroblast Growth Factor Receptors in Brain Trophism and Plasticity

Valentina Di Liberto[1], Giuseppa Mudò[1], Kjell Fuxe[2] and Natale Belluardo[1,*]

[1]*Department of Experimental Biomedicine and Clinical Neuroscience, University of Palermo, corso Tukory 129, IT-90134, Palermo Italy;* [2]*Karolinska Institutet, Department of Neuroscience, Retzius väg 8, Stockholm 17177, Sweden*

**Abstract:** Acetylcholine, acting on both nicotinic receptors (nAChRs) and muscarinic receptors (mAChRs), plays a role in the regulation of synaptic plasticity, being involved in the regulation of cellular processes and cognitive functions, such as learning, memory and attention. Recently, G protein coupled receptors (GPCRs), including mAChRs, have been reported to transactivate tyrosine-kinase receptors (RTK), such as epidermal growth factor receptor (EGFR), and initiate their intracellular signaling. In this minireview we have first analysed the RTK transactivation mechanisms, involving cholinergic receptors, and thereafter the interplay between AChR and neurotrophic factor systems built up by FGF2 and fibroblast growth factor receptor 1 (FGFR1). Although mAChR and FGFR1 activate common signaling pathways, playing similar roles in the regulation of central nervous system (CNS) plasticity and trophism, this analysis revealed that at the present there are no data reporting an involvement of cholinergic receptors in the FGFR1 transactivation. However, here we reported preliminary results on FGFR1 transactivation by mAChRs, suggesting a possible interaction between mAChR and neurotrophic factor receptors, with potential relevance for cognitive functions.

**Keywords:** FGFR1, G protein coupled receptor, Muscarinic receptors, Nicotinic receptors, Receptor-receptor interaction, Synaptic plasticity, Transactivation, Tyrosine-kinase receptors.

## 1. INTRODUCTION

The aim of this minireview was to reviewer the present knowledge of receptor interactions involving cholinergic receptors and neurotrophic factor receptor FGFR1. We first analyzed the acetylcholine (Ach) receptor expression and functions, and, following an analysis of the literature on crosstalk between G protein coupled receptors (GPCRs) and tyrosine-kinase receptors (RTKs), we focused our work on general data showing RTK transactivation by AChR activation. Subsequently, we have collected evidence for an interplay between cholinergic receptors and FGF2/FGFR1 system, mediating neuronal survival, trophism and plasticity. In the last part of this minireview we have examined the hypothesis of FGFR1 and AChR interactions and provided preliminary data for such events from *in vivo* and *in vitro* studies.

## 2. OVERVIEW ON ACETYLCHOLINE RECEPTOR EXPRESSION AND FUNCTIONS

The role of Ach in cognitive functions has been well characterized [1-3]. In addition to a general role in learning [4, 5] and memory [6, 7], recent studies have also provided support for a role of cortical ACh in attention and detection of behavioral significant stimuli [8-10]. The main role of ACh in mnemonic function is very well showed in Alzheimer's disease (AD), where deficits in attention, learning and memory are associated to dysfunction of the cholinergic system [11, 12]. Ach effects are mediated by two classes of specific membrane receptors: nicotinic receptors (nAChRs) and muscarinic receptors (mAChRs).

### 2.1. mAChR

mAChR are heptaelical metabotropic receptors coupled to G proteins and to date, five genes encoding five subtypes of mAChR (M1-5) have been identified [13-16]. In general, although the specificity is not absolute, the M1, M3, and M5 receptors activate phospholipase C (PLC), while M2 and M4 receptors inhibit adenylyl cyclase [14, 17]. In addition to their canonical signaling pathways, mAChR can also regulate the mitogen-activated protein kinases (MAPKs), phosphoinositide- 3-kinase, RhoA, and Rac1 [15, 18, 19]. Specifically, the M1, M3, and M5 receptors stimulate pathways involving phospholipase A2 and D, TRK, calcium channels, whereas M2 and M4 receptors may signal using phospholipase A2 [20]. M1 receptors are primarily located postsynaptically and found throughout the brain with the highest concentrations in cerebral cortex and hippocampus [21-24]. M2 receptors can be found mainly in brainstem, nucleus basalis, cerebellum and thalamus where they are located both pre- and post-synaptically [23, 25, 26]. M3 receptors show a similar distribution to M1 receptors, but with lower level of expression [23, 27]. M4 receptors are mainly found in the striatum [22], often associated with dopaminergic receptors [28], while M5 receptors show low expression levels in the hippocampus, substantia nigra, and ventral tegmental area [29, 30]. Different type of synaptic plasticity can be induced by mAChRs [31]. In this context, activation of presynaptic or

*Address correspondence to this author at the Department of Experimental Biomedicine and Clinical Neuroscience, University of Palermo, corso Tukory 129, IT-90134, Palermo Italy; Tel: +390916555849; Fax: +3909123860714, E-mail: natale.belluardo@unipa.it

1875-5550/14 $58.00+.00

postsynaptic mAChRs either enhances or reduces long term potentiation (LTP) in the hippocampus [32-42]. Indeed, the current AD treatments are also based on restoration of cholinergic signaling by inhibiting the cholinesterase enzyme and increasing Ach synaptic levels [43-47] or by using cholinergic agonists, especially M1, such as AF102B and AF267B [48, 49], and nicotinic receptor subtype α7 agonists [50-52].

In addition to the well-documented role in regulating synaptic plasticity, ACh, acting on muscarinic receptors, modulates different physiological responses, including apoptosis, neural stem cells and progenitors proliferation and neuronal differentiation [53-56], inhibit apoptosis and exert protective effects in many cell lines and primary cell cultures [57-62]. For example, carbachol acting via muscarinic receptors, activates PI-3 kinase and Erk1/2, resulting in stimulation of DNA synthesis in neural progenitor cells [18, 63]. Systemic administration of galantamine, an acetylcholinesterase inhibitor, promotes protection of retinal ganglion cells soma and axons in a rat glaucoma model through the activation of M1 and M4 muscarinic acetylcholine receptors [64]. Pilocarpine, a muscarinic agonist, exerts protective effects against hypoxia-induced apoptosis in retinal ganglion cells [65]. mAChRs inhibit apoptosis both by activation of PI3-kinase and its downstream targets, protein kinase B (PKB)/Akt and MAPK/ERK [66-68] and by transcription of anti-apoptotic protein [69]. Moreover, activation of mAChR can modulate the production or/and release of neurotrophic factors in neurons, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which in turn could mediate neurotrophic/neuroprotective functions and the induction of hippocampal LTP as well [70-73].

### 2.2. nAChR

nAChRs are assembled as pentamers of at least 17 identified subunits, that can exist as homopentamers of α (α7–α10) subunits or heteropentamers of α (α2–α6) and β (β2–β4) subunits [74]. In the central nervous system (CNS), the α4β2 and α7 nAChRs are the two main expressed nAChR subtypes [75], but they have diverse functional properties [76]. Activation of nAChRs, particularly the α7 subtype, with exogenous ligands enhances synaptic plasticity in the CA1 [77-79], CA3 [80] and dentate gyrus [81] of the hippocampus and in deep layers of the entorhinal cortex [82]. nAChRs can also control many important cell functions such as proliferation, survival and apoptosis [83, 84]. In neurons, the α7 nicotinic receptor activates PI3-kinase-Akt pathway, which protects neurons against apoptotic cell death triggered by beta-amyloid fragments, suggesting that nicotinic agents may be useful in the treatment of AD and other neurodegenerative conditions [85, 86]. Moreover, α7 nicotinic acetylcholine receptor mediates neuroprotection against dopaminergic neuron loss in an MPTP mouse model [87], against hypoxia [88] and glutamate neurotoxicity in rat cortical cultured neurons [89]**.** The involvement of α7 nicotinic receptor in neuroprotection, both *in vivo* and *in vitro*, is confirmed by the fact that mice with mutation of the nAChR-α7 subtype show an increase of neuronal apoptosis and die at birth [90]. Furthermore, nicotinic agonists protect against neuronal death in several experimental models, such as nucleus magnocellularis lesions, hippocampal CA1 subregion ischemia [91] and fimbrial transaction [92]. All these anti-apoptotic effects can be mediated by activation of PKC, PKA Erk1/2, downregulation of the tumor suppressor p53 [93, 94] and the activation of transcription factors, such as Elk1, nuclear factor-κB (NF-κB), and cAMP response element (CRE)-binding factor (CREB), which in turn can regulate neurotrophic factors expression [95-97]. In fact, activation of nicotinic receptors can stimulate release of neurotrophic factors, such as FGF-2, BDNF [98] and insulin-like growth factor 2 (IGF-2) [99].

Nicotinic receptors can also modulate precursor cell proliferation as well. For example, we have previously found an enhancing effect of nAChR activation by acute intermittent nicotine treatment on precursor cell proliferation in the subventricular zone (SVZ) of the adult rat mediated by FGF-2 via FGFR-1 activation [100-102]. Activation of α4/β2 nAChR in undifferentiated neural progenitors promotes neuronal differentiation into particular lineages in fetal rodent neocortex [103] and stimulation of α4/α7-nAchR leads to a significant increase in the proliferation of mouse pluripotent stem cells [104]. It has been showed that nicotine-induced cell proliferation depend on β-arrestin, which activates Src that subsequently leads to binding of Raf-1 kinase to the tumor suppressor retinoblastoma (Rb) protein, producing cell cycle entry [105]. Moreover, the decline of hippocampal cell proliferation in mice lacking the nAChR-$\beta_2$ subunit [106] further demonstrates that nAChRs may play a direct role in the regulation of neurogenesis. nAChRs are also expressed on O2A oligodendrocyte precursors and may regulate cell migration, survival and differentiation [107].

Taken together, all this experimental evidence indicates a crucial role for the cholinergic system in regulating many vital cell functions, from proliferation to survival, being involved in important CNS mechanisms, such as neuroprotection, synaptic plasticity and neurogenesis. Therefore ACh, by both nAChR and mAChR activation, plays a vital role in cognitive functions, such as attention, learning and memory.

## 3. CROSSTALK BETWEEN GPCR AND RTK

Recently, it has become more evident that GPCRs and RTKs, by activation of a common cell signaling, do not work in an individual fashion, and the cross-communication between them permits cells to integrate information from diverse sources, providing a complex control with different regulatory mechanisms [108]. In fact, cumulating data demonstrated that, in addition to classical second messenger-regulated mechanisms, GPCRs show a growth-promoting activity involving RTKs and related downstream signaling events [109-112]. These observations have led to the transactivation concept, which, according to the definition proposed by Little *et al.*, 2011 [113] indicates "the agonist occupancy of its cognate GPCR complex which leads in a relatively short time and in the absence of *de novo* protein synthesis to the activation of RTK and cytosolic generation of the immediate downstream signals". Importantly, crosstalk between RTKs and GPCRs takes place bidirectionally, thus several evidence has revealed an involvement of GPCR signaling molecules (e.g., heterotrimeric G proteins and arrestins) in signal transduction mediated by RTK [114-116]. Furthermore, RTKs can be transactivated not only by GPCR agonists, but also by specific ligands of RTKs; as example (IGF-

1) transactivates the EGF receptor, leading to activation of ERK and phosphorylation of BAD, a member of the Bcl-2 protein family, and therefore contributing to IGF-1 antiapoptotic effects [117,118].

At present, two type of RTK transactivation by GPCRs have been revealed. In the first one, defined 'triple membrane bypass', the GPCR stimulation activates surface bound matrix metalloproteinases (MMPs) which in turn cleaves the RTK ligand precursor leading to active ligand and subsequent action on the receptor. An example of this ligand-dependent mechanism is the MMP mediated cleavage of heparin-binding EGF (HB-EGF), which activates the EGFR [119-122]. The second type of transactivation is ligand-independent and involves the physical interaction of the GPCR and the transactivated RTK [111, 123, 124] or the phosphorylation of the transactivated RTK by a tyrosine kinase downstream of GPCR signaling [125, 126]. In the last case, the GPCR may activate tyrosine kinases mediators, e.g. the Src family kinases [127, 128], which directly may induce the receptor phosphorylation. For instance, Src-dependent RTK transactivation has been involved in the activation of TrkA receptor by adenosine [129], while a transactivation mediated by a receptor-receptor interaction has been demonstrated for IGF-1R and GABA(B) receptor in primary neurons [130], for Adenosine A2A receptor and FGFR in PC12 cells and primary neuronal cultures [131], and for serotonin receptor 1A (5-HT1A) and FGFR1in the rat hippocampus. [123].

The generation of reactive oxygen species (ROS) may also regulate intracellular cascades that control the activity of RTKs [126]. For example, ROS induce release of zinc, the increased cytosolic zinc transactivates TrkB, through a Src family kinase-dependent mechanism. This transactivation may enhance Shc signaling downstream from TrkB, promoting survival effects in cultured rat cortical neurons [132] and playing a significant role in LTP at the mossy fiber-CA3 synapses [133].

Recently it has been demonstrated that GPCR agonists, such as Endothelin-1 and thrombin, can also transactivate the serine/threonine kinase cell surface receptor for transforming growth factor-β (Alk5) [134, 135].

A growing number of transactivation examples have been described and some of them involve neurons and play an important role in the regulation of CNS functions. EGFR, that has been involved in cell survival, proliferation and differentiation [136], can be transactivated by several GPCR agonists, such as angiotensin II, endothelin-1 and phenylepherine [137], bradykinin [138], lysophosphatidic acid, endothelin, thrombin, bombesin and carbachol [120, 122, 139, 140], lipopolysaccharide [141, 142], gonadotropin-releasing hormone [143] and a2-adrenoceptor [144]. This transactivation may be MMP-dependent or Src-dependent and mediate many of growth-promoting effects of EGFR. In CNS, EGFR can be transactivated by adenosine $A_1$ receptor through a mechanism dependent on PI3 kinase and Src kinase, that confers a neuroprotective effect in primary cortical neuron [145] and by P2Y purine receptors through a mechanism MMP-dependent and mediating the proliferation of glial cells [146]. Fluoxetine-mediated serotonin receptor 2B (5-HT2B) stimulation in astrocytes causes EGFR transactivation by MMP-dependent shedding of EGF and a subsequent ERK phosphorylation [147]. In cultured rat cortical astrocytes ERK2 phosphorylation following activation of metabotropic glutamate receptor 5 (mGluR5) is dependent on EGFR activation mediated by a Src kinase [148].

Platelet-derived growth factor β (PDGF β) receptor, another potent RTK responsible for angiogenesis, cell growth, proliferation, changes in cell shape, motility, migration, and embryonic development [149], can be transactivated by several GPCRs. Serotonin (5-HT) receptor can transactivate the PDGFβ receptor in pulmonary artery smooth muscle cells and in neuronal cells [150-152]. Both D2 [153] and D4 dopamine receptors [154] can transactivate PDGFβ receptor and this activation by D4 dopamine receptor may lead to depression of excitatory neurotransmission mediated by NMDA receptors in CA1 neurons of the hippocampus, suggesting that RTK transactivation might also modulate synaptic transmission [154]. Using SH-SY5Y neuroblastoma cells and primary cortical neurons it has been shown that 5-HT may increase the phosphorylation of PDGFβ receptors through 5-HT1A receptors and this activation is mediated by Src tyrosine kinase [152]. This crosstalk between 5-HT receptor and a growth factor receptor suggest that some effects of antidepressant drugs could be mediated by the activation of RTKs. Furthermore, PDGFβ can be transactivated by GPCR different agonists such as angiotensin II [155, 156], sphingosine-1-phosphate [157], lysophosphatidic acid [158, 159], and leukotrienes [160].

Several data have shown that IGF-1 is involved in brain development [161] and neuronal survival [162] by binding to tyrosine kinase receptor IGF-1R and activating the PI3 kinase/Akt signaling cascade [163]. $GABA_B$ receptor can transactivate IGF-1R, through a ligand-independent pathway involving $G_{i/o}$-protein and PLC/$Ca^{2+}$-dependent FAK1, leading to Akt phosphorylation and survival signaling in cerebellar granule neurons [164].

The neurotrophins (NGF, BDNF, Neurotrophin-3 NT3 and meurotrophin-4 NT4) control a number of aspects of survival, development, and function of neurons, such as synaptic plasticity, axon outgrowth, morphology, and differentiation, in both the central and peripheral nervous systems. Biological effects of neurotrophins are mediated by one or more of members of tyrosine kinases receptor family, including TrkA, TrkB, and TrkC [165, 166]. Antidepressant drugs can transactivate TrkB receptor in the adult rodent brain [167], producing in the anterior cingulate cortex and hippocampus a rapid autophosphorylation of TrkB and consequently activation of PLC and increase in the phosphorylation of CREB protein [168]. Thus, neurotrophic receptor signaling activated by antidepressants may induce synaptic connectivity with antidepressive effects and mood recovery, suggesting that targeting neurotrophin receptor might be a rational strategy to treat depression [169-171]. Adenosine A2A receptor determine trophic effects through the TrkA receptor in PC12 cells, and of TrkB in hippocampal neurons, that is dependent on mobilization of intracellular Ca2+ and activation of Src tyrosine kinases [172-174]. Moreover, adenosine A2A receptor contributes to motoneuron survival by transactivating TrkB [175] and dopamine receptors (D1R and D2R) transactivate TrkB in striatal neurons [176]. Giv-

ing the central role of dopamine receptors in the action of drugs used to treat some psychiatric conditions [177], transactivation of TrkB by dopamine receptors activation should be taken in account for psychiatric mood disorders and schizophrenia treatment [170].

The neurotrophic system FGF2/FGFR1, extensively described below, regulates many functions of the CNS, such as brain development, by promoting cell proliferation, survival, migration, and differentiation [178-182], adult neurogenesis [101, 102, 183] and regenerative plasticity following brain injury [184]. Several examples of FGFRs transactivation have been described in the last years. In rat C6 glioma cells Mu-opioid receptor (MOR), but not kappa-opioid receptor (KOR), has been found to transactivate the FGFR1, causing a rapid increase in ERK1/2 phosphorylation [185], and 5-HT2 receptor induces a Src-dependent FGFR2 transactivation and consequently GDNF mRNA expression [186]. Recently, we have demonstrated that 5-HT1A agonist may induce transactivation of the FGFR1 through the formation of an heteroreceptor complex in the rat hippocampus, thus enhancing neuroplasticity [123]. Finally, the cannabinoid 1 receptor (CB1R) agonist methanandamide induces transactivation of FGFR1 via Src and Fyn, which drives an amplification wave in ERK1/2 activation, leading to neuronal differentiation in embryonic cortical neurons [187].

All together, these data on cross-communication between GPCR and RTK signaling systems testify the presence in cells of multiple regulatory mechanisms aimed to integrate information from diverse sources [108, 109]. In other words, the apparent primary response, such as the generation of a phosphorylated transcription factor, may not arise solely from the actions of a protein kinase, but may involve the earlier activation of a GPCR and a transactivation mechanism. Functionally, this transactivation mechanism implicates that GPCR may be a potential novel therapeutic target to enhance for example cell survival or to limit cell proliferation.

## 4. CROSSTALK BETWEEN mAChRs AND RTKs

Crosstalk between mAChRs and RTKs has been demonstrated in several experimental models. In particular, communication between mACh receptor and the EGFR has been shown as critical element for GPCR-induced signaling in many cell types [120]. In the colon cancer cell line NCI-H508, EGFR transactivation by mAChRs (M3) has been shown to be the major pathway responsible for ERK1/2 activation and cell proliferation [188]. Similarly, carbachol activates ERK1/2 in T84 colon cancer cell line via a mechanism involving transactivation of the EGFR, and this pathway constitutes an inhibitory mechanism by which chloride secretory responses to carbachol may be negatively regulated [189]. Carbachol may transactivate EGFR by a pathway involving increase in intracellular Ca(2+) and calmodulin, PYK-2, a metalloproteinase-dependent extracellular release of TGF-alpha and Src activation [190, 191]. EGFR is also involved in mAChR mediated activation of ERK1/2 and the subsequent proliferation of SNU-407 colon cancer cells [192]. In human salivary epithelial HSY cell line, muscarinic agonist pilocarpine induces ERK activation via Src-mediated EGFR transactivation, occurring mainly through the M3 receptor subtype [193]. In rabbit, muscarinic receptor transactivation of EGFR, by inducing ROS generation mediated by a metalloproteinase-dependent cleavage of proHB-EGF, shedding of HB-EGF, has been linked to cardioprotection [194]. In stable transfected human 293 cells, M1 AChR signaling transactivates EGFR and modulates the voltage-gated $K^+$ channel termed Kv1.2 [195], suggesting a new role for the EGFR in regulation of membrane excitability and neurotransmitter receptor signaling [196]. In COS-7 cells transiently expressing M2 AChR and in SH-SY5Y neuroblastoma cells endogenously expressing M2 AChR, carbachol induces EGFR transactivation [197].

In addition to EGFR, other RTK has been found to be transactivated by mAChR. Particularly, it has been shown that mAChR agonists carbachol and pilocarpine may activate mammalian target of rapamycin (mTOR) through a vascular endothelial growth factor receptor-2 (VEGFR2) dependent mechanism in serum starved SK-N-SH human neuroblastoma cells [198] and this mechanism may be involved in neuroprotection against stress conditions [199-201], or apoptotic cell death [202]. Lastly, recently it has been described that galantamine and donepezil, two acetylcholinesterase inhibitors, are capable of rapidly activating TrkA and TrkB receptors in the mouse hippocampus and the downstream signaling AKT and CREB, without regulating BDNF or NGF synthesis [203], suggesting also a possible interplay between mAChR and neurotrophic factor receptors.

## 5. CROSSTALK BETWEEN IONOTROPIC RECEPTORS AND RTKs

In contrast to GPCRs, little evidence has emerged on the crosstalk between ionotropic receptors and RTKs. However, it has been demonstrated that P2X7 receptor stimulation increases the transactivation of the EGFR and the phosphorylation of ERK and Elk-1 [204]. Furthermore, the combined activation of ionotropic and metabotropic glutamate receptors located on hypothalamic astroglial cells induces physical approximation of ErbB receptors (ErbB1 and ErbB4) and their respective ligands (TGFα and neuregulin-β) on the cell membrane of astrocytes and leads to a metalloproteinase-dependent cleavage of ErbB ligand precursors, which in turn transactivate astrocytic ErbB receptors. This complicated pathway may represent a mechanism that the neuroendocrine brain uses during sexual development [205]. However, at the present, there are no data demonstrating an involvement of ionotropic nicotinic receptors in the transactivation of RTKs.

## 6. FGF2/FGFR1 NEUROTROPHIC SYSTEM

FGF2 is a neurotrophic factor that regulates many functions of the central nervous system such as brain development, by promoting fetal and postnatal cell proliferation, survival, migration, and differentiation [178-182], adult neurogenesis [101, 102, 183], and regenerative plasticity following brain injury [184]. FGF2 has been largely studied as a potent regulator of proliferation and differentiation for multipotent neural progenitors isolated from adult SVZ and sub-granular zone (SGZ) of rodent brain [102, 206-211]. In addition, FGF2 may drive rat embryonic stem cells differentiation into neurons [182]. FGF2 activates also the neurogenic potential of progenitor cells isolated from cerebral cortex, striatum, and substantia nigra of rat brain [212-214]. FGF2 enhances production

and dendritic growth of new dentate granule cells in hippocampus [215], increases neurite elongation in cultured hippocampal cells [216, 217] and sprouting of axon terminals of the cholinergic septo-dentate pathway following unilateral entorhinal lesions [218]. In addition, FGF2 plays a critical role in regulating synaptic plasticity [219].

All these FGF2 effects are mediated by activation of cell-surface RTK, including four different subtypes of FGFR in rodents [220], and five FGFR in humans [221]. Ligand binding to FGFR leads to the formation of a receptor complex, consisting of two FGF molecules bound to a receptor, which are linked by a heparan sulfate proteoglycan molecule [222, 223] and to consequent receptor autophosphorylation. There are seven tyrosine residues (Tyr463, Tyr583, Tyr585, Tyr653, Tyr654, Tyr730 and Tyr766) in the cytoplasmic tail of FGFR1 that can be substrates for phosphorylation and among them Tyr653 and Tyr654 are important for the catalytic activity of the activated FGFR and are essential for signaling [224]. Activation of FGFR induces the activation of three major pathways: phospholipase C/PKC, Ras/ MAPK (including ERK, JNK and p38), and PI3K/protein kinase B ( also called Akt) [225]. In the adult CNS, FGFR1, FGFR2 and FGFR3 are found to be highly expressed in the diencephalon and telencephalon and moderately expressed in the mesencephalon, metencephalon and myelencephalon [226]. FGFR1 is expressed mainly in neuronal populations of the adult CNS [227, 228], but has also been detected in astrocytes of white matter tracts [229]. In contrast to FGFR1, FGFR2 and FGFR3 are primarily expressed in glial cells [228, 230]. The FGFR4, however, is strongly expressed in the lateral habenular nucleus [226, 231].

## 7. NICOTINIC AND MUSCARINIC RECEPTOR AGONISTS EFFECT ON FGF/FGFR SYSTEM

Evidence for a complex interplay between cholinergic receptors, especially nAChR, and FGF2/FGFR1 system, mediating neuronal survival, trophism and plasticity, has appeared in the last years. We have previously demonstrated that acute intermittent nicotine treatment or nicotinic agonists such as epibatidine and ABT-594 treatment, lead to a substantial upregulation of FGF2 mRNA and protein levels in the cerebral cortex, the hippocampal formation, the striatum, the ventral midbrain [232-235] and in the hippocampal neurons [236]. Furthermore, we have demonstrated that intermittent nicotine treatment, by increasing FGF2, significantly enhances neuronal precursor cell proliferation in the SVZ of adult rat [101] and restores aged-dependent decline of neuronal precursor cell proliferation levels nearly to those found in the young adult rat [237]. Stimulation of nAChR in cultured adrenal medullary cells increases FGF-2 gene expression [238], mediated by adenylate cyclase or PKC and dependent on nuclear interaction of transactivating factors with a novel cis-acting element [239]. Nicotine is also a potent regulator of FGF2 production and release by aortic smooth muscle cells [240] and in endothelial cells [241]. In contrast, a two-week continuous infusion with nicotine in the intact rat leads to substantial and dose-related reductions of FGF2 mRNA levels in the ventral midbrain [242] and acute intermittent nicotine treatment produces a significant reduction in the total number of nuclear FGF2 immunoreactive astroglial profiles in the substantia nigra [243]. Very few data report the modulation of FGF2 expression by muscarinic agents: in human and mouse scleral fibroblasts, atropine seems to increase FGF2 in a dose-dependent manner, while carbachol seems to decrease FGF2 [244].

In conclusion, an interplay between cholinergic receptors and FGF2/FGFR1 system has been demonstrated, especially involving the regulation of FGF2 production by nicotinic receptors, enhancing neuroprotection, proliferation and synaptic changes in target structures, such as hippocampus.

## 8. FGFR1 TRANSACTIVATION BY AChR AGONISTS

Although mAChR and FGFR1 activate common signaling pathways, such as PLC/PKC, Ras/ MAPK and PI3K/AKt, playing similar roles in the regulation of CNS plasticity and trophism, as above mentioned, at the present there are no data reporting an involvement of ionotropic and metabotropic AChRs in the FGFR1 transactivation. Extending our previous studies on FGFR1 transactivation by 5-HT1A agonists [123], and given that mAChR agonists can transactivate a RTK, such as EGFR, we have hypothesized that AChRs could transactivate FGFR1 and enhance trophic effects and neural plasticity in hippocampal formation. Both AChRs (muscarinic and nicotinic subtypes) and FGFR1 [226] are expressed in the hippocampus. In order to verify FGFR1 transactivation by AChR activation in the hippocampus we have undertaken an *in vivo* and *in vitro* study to verify the effects of acute treatment with mAChR or nAChR agonists on the FGFR1 phosphorylation. Here, we reported preliminary studies showing transactivation of FGFR1 following mAChR activation. A time course study following *in vivo* acute treatment with Pilocarpine (3mg/kg) revealed at 7.5 min. from treatment a significant increase of FGFR1 phosphorylated, that already returned to basal levels at 15 min. from treatment. Pretreatment with atropine abolished the pilocarpine effect on FGFR1 phosphorylation. By contrast, a time-course study following acute *in vivo* treatment with nicotine (1 mg/kg; single dose) did not show a change in the FGFR1 phosphorylation levels in the hippocampus. This result does not support the acute involvement of nAChR on FGFR1 transactivation. However, as reported above, acute intermittent treatment with nicotine has shown that nAChR interact with the FGF-2/FGFR1 system at least by modulating FGF-2 cell expression and release.

Using hippocampal primary culture, we performed a time-course and dose effect study of carbachol effect on FGFR1 phosphorylation and data showed an increase of FGFR1 phosphorylation levels following treatment with carbachol for 5 min and at doses ranging from 10 μM to 50 μM. This result, although very preliminary, suggests the existence of a transactivation mechanisms involving mAChRs and FGFR1 in the hippocampus. This hypothesis is supported by a recent evidence showing the existence of an FGFR1-M3 heteroreceptor complex in the dentate gyrus but not in other region from the hippocampus [245], suggesting a specific transactivation mechanism mediated by the physical association between the two receptors.

Development of this investigation will contribute to advance the understanding of cholinergic drugs mechanism and to develop new strategies not only for Alzheimer disease but also for mild form of memory deficit.

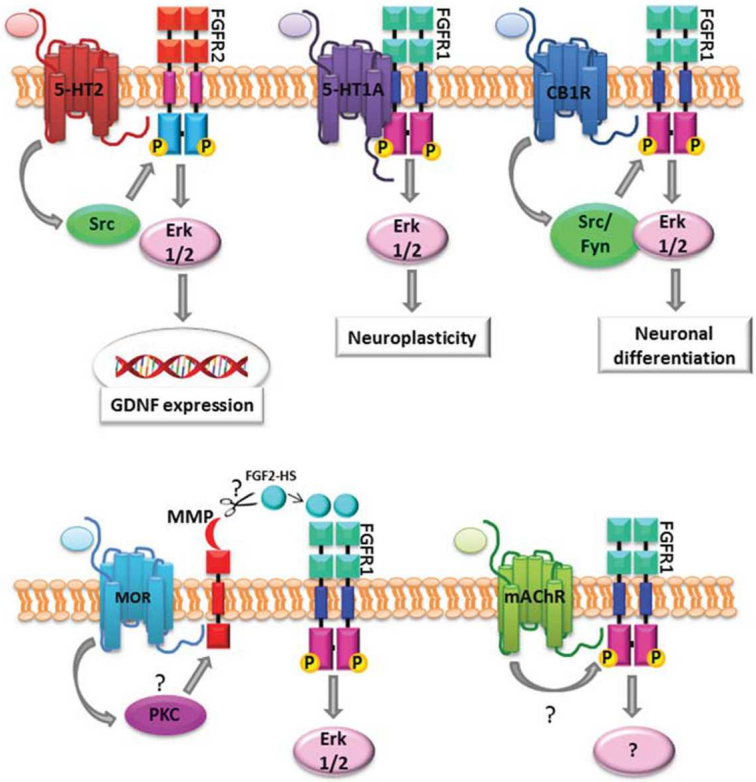


**Fig. (1).** Scheme showing the mechanism of FGFR transactivation by different GPCRs. 5-HT2 receptor activation induces a Src-dependent FGFR2 transactivation that consequently upregulates GDNF expression via Erk1/2 [186]. 5-HT1A agonists induce the transactivation of the FGFR1 through the formation of a heteroreceptor complex, enhancing neuroplasticity via Erk1/2 [123]. CB1R activation, via Src and Fyn, induces the transactivation of FGFR1, leading to neuronal differentiation via ERK1/2 [187]. MOR activation, probably through a mechanism involving $Ca^{2+}$- and PKC-mediated MMP activation, causes the shedding of FGF2- heparan sulfate (FGF2-HS) and transactivates FGFR1 leading to a rapid increase in ERK1/2 phosphorylation [185]. mAChRs activation transactivates FGFR1 (see text).

## CONCLUSION

Taken together, the experimental evidence indicates a growing crucial role for a cross-communication between GPCR and RTK signaling systems in regulating many vital cell functions from proliferation to survival, and being involved in important features of CNS, such as neuroprotection and synaptic plasticity. In this work we reviewed data reporting FGFR1 transactivation by different GPCR, including mAChR as shown in the scheme of (Fig. **1**). New data, although preliminary, reported in the present review opens up also a possible interplay between mAChR and neurotrophic factor systems where transactivation of RTKs may play a crucial role leading to increases in cognitive functions such as learning, memory and attention.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

[1] Bentley, P.; Driver, J.; Dolan, R.J. Cholinergic modulation of cognition: insights from human pharmacological functional neuroimaging. *Prog. Neurobiol.*, **2011**, *94*(4), 360-388.

[2] Blokland, A. Acetylcholine: a neurotransmitter for learning and memory? *Brain Res. Brain Res. Rev.*, **1995**, *21*(3), 285-300.

[3] Sarter, M.; Bruno, J.P. Cognitive functions of cortical acetylcholine: toward a unifying hypothesis. *Brain Res. Brain Res. Rev.*, **1997**, *23*(1-2), 28-46.

[4] Robinson, L.; Platt, B.; Riedel, G. Involvement of the cholinergic system in conditioning and perceptual memory. *Behav. Brain Res.*, **2011**, *221*(2), 443-465.

[5] Deiana, S.; Platt, B.; Riedel, G. The cholinergic system and spatial learning. *Behav. Brain Res.*, **2011**, *221*(2), 389-411.

[6] Micheau, J.; Marighetto, A. Acetylcholine and memory: a long, complex and chaotic but still living relationship. *Behav. Brain Res.*, **2011**, *221*(2), 424-429.

[7] Hasselmo, M.E.; Anderson, B.P.; Bower, J.M. Cholinergic modulation of cortical associative memory function. *J. Neurophysiol.*, **1992**, *67*(5), 1230-1246.

[8] Picciotto, M.R.; Higley, M.J.; Mineur, Y.S. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. *Neuron*, **2012**, *76*(1), 116-129.

[9] Parikh, V.; Kozak, R.; Martinez, V.; Sarter, M. Prefrontal acetylcholine release controls cue detection on multiple timescales. *Neuron*, **2007**, *56*(1), 141-154.

[10] Klinkenberg, I.; Sambeth, A.; Blokland, A. Acetylcholine and attention. *Behav. Brain Res.*, **2011**, *221*(2), 430-442.

[11] Schliebs, R.; Arendt, T. The cholinergic system in aging and neuronal degeneration. *Behav. Brain Res.*, **2011**, *221*(2), 555-563.

[12] Auld, D.S.; Kornecook, T.J.; Bastianetto, S.; Quirion, R. Alzheimer's disease and the basal forebrain cholinergic system: relations to beta-amyloid peptides, cognition, and treatment strategies. *Prog. Neurobiol.*, **2002**, *68*(3), 209-245.

[13] Wess, J. Molecular biology of muscarinic acetylcholine receptors. *Crit Rev. Neurobiol.*, **1996**, *10*(1), 69-99.

[14] Caulfield, M.P.; Birdsall, N.J. International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. *Pharmacol. Rev.*, **1998**, *50*(2), 279-290.

[15] Nathanson, N.M. A multiplicity of muscarinic mechanisms: enough signaling pathways to take your breath away. *Proc. Natl. Acad. Sci. U. S. A*, **2000**, *97*(12), 6245-6247.

[16] Hulme, E.C.; Birdsall, N.J.; Buckley, N.J. Muscarinic receptor subtypes. *Annu. Rev. Pharmacol. Toxicol.*, **1990**, *30*, 633-673.

[17] Matsui, M.; Yamada, S.; Oki, T.; Manabe, T.; Taketo, M.M.; Ehlert, F.J. Functional analysis of muscarinic acetylcholine receptors using knockout mice. *Life Sci.*, **2004**, *75*(25), 2971-2981.

[18] Spindel, E.R. Muscarinic receptor agonists and antagonists: effects on cancer. *Handb. Exp. Pharmacol.*, **2012**, *208*, 451-468.

[19] Marinissen, M.J.; Gutkind, J.S. G-protein-coupled receptors and signaling networks: emerging paradigms. *Trends Pharmacol. Sci.*, **2001**, *22*(7), 368-376.

[20] Felder, C.C. Muscarinic acetylcholine receptors: signal transduction through multiple effectors. *FASEB J.*, **1995**, *9*(8), 619-625.

[21] Hohmann, C.F.; Potter, E.D.; Levey, A.I. Development of muscarinic receptor subtypes in the forebrain of the mouse. *J. Comp Neurol.*, **1995**, *358*(1), 88-101.

[22] Levey, A.I. Immunological localization of m1-m5 muscarinic acetylcholine receptors in peripheral tissues and brain. *Life Sci.*, **1993**, *52*(5-6), 441-448.

[23] Flynn, D.D.; Mash, D.C. Distinct kinetic binding properties of N-[3H]-methylscopolamine afford differential labeling and localization of M1, M2, and M3 muscarinic receptor subtypes in primate brain. *Synapse*, **1993**, *14*(4), 283-296.

[24] Volpicelli, L.A.; Levey, A.I. Muscarinic acetylcholine receptor subtypes in cerebral cortex and hippocampus. *Prog. Brain Res.*, **2004**, *145*, 59-66.

[25] Zhang, W.; Basile, A.S.; Gomeza, J.; Volpicelli, L.A.; Levey, A.I.; Wess, J. Characterization of central inhibitory muscarinic autoreceptors by the use of muscarinic acetylcholine receptor knock-out mice. *J. Neurosci.*, **2002**, *22*(5), 1709-1717.

[26] Rouse, S.T.; Thomas, T.M.; Levey, A.I. Muscarinic acetylcholine receptor subtype, m2: diverse functional implications of differential synaptic localization. *Life Sci.*, **1997**, *60*(13-14), 1031-1038.

[27] Levey, A.I.; Edmunds, S.M.; Heilman, C.J.; Desmond, T.J.; Frey, K.A. Localization of muscarinic m3 receptor protein and M3 receptor binding in rat brain. *Neuroscience*, **1994**, *63*(1), 207-221.

[28] Weiner, D.M.; Levey, A.I.; Brann, M.R. Expression of muscarinic acetylcholine and dopamine receptor mRNAs in rat basal ganglia. *Proc. Natl. Acad. Sci. U. S. A*, **1990**, *87*(18), 7050-7054.

[29] Vilaro, M.T.; Palacios, J.M.; Mengod, G. Localization of m5 muscarinic receptor mRNA in rat brain examined by in situ hybridization histochemistry. *Neurosci. Lett.*, **1990**, *114*(2), 154-159.

[30] Reever, C.M.; Ferrari-DiLeo, G.; Flynn, D.D. The M5 (m5) receptor subtype: fact or fiction? *Life Sci.*, **1997**, *60*(13-14), 1105-1112.

[31] Brown, D.A. Muscarinic acetylcholine receptors (mAChRs) in the nervous system: some functions and mechanisms. *J. Mol. Neurosci.*, **2010**, *41*(3), 340-346.

[32] Leung, L.S.; Shen, B.; Rajakumar, N.; Ma, J. Cholinergic activity enhances hippocampal long-term potentiation in CA1 during walking in rats. *J. Neurosci.*, **2003**, *23*(28), 9297-9304.

[33] Seeger, T.; Fedorova, I.; Zheng, F.; Miyakawa, T.; Koustova, E.; Gomeza, J.; Basile, A.S.; Alzheimer, C.; Wess, J. M2 muscarinic acetylcholine receptor knock-out mice show deficits in behavioral flexibility, working memory, and hippocampal plasticity. *J. Neurosci.*, **2004**, *24*(45), 10117-10127.

[34] Cobb, S.R.; Davies, C.H. Cholinergic modulation of hippocampal cells and circuits. *J. Physiol*, **2005**, *562*(Pt 1), 81-88.

[35] Shinoe, T.; Matsui, M.; Taketo, M.M.; Manabe, T. Modulation of synaptic plasticity by physiological activation of M1 muscarinic acetylcholine receptors in the mouse hippocampus. *J. Neurosci.*, **2005**, *25*(48), 11194-11200.

[36] Doralp, S.; Leung, L.S. Cholinergic modulation of hippocampal CA1 basal-dendritic long-term potentiation. *Neurobiol. Learn. Mem.*, **2008**, *90*(2), 382-388.

[37] Gu, Z.; Yakel, J.L. Timing-dependent septal cholinergic induction of dynamic hippocampal synaptic plasticity. *Neuron*, **2011**, *71*(1), 155-165.

[38] Gu, Z.; Lamb, P.W.; Yakel, J.L. Cholinergic coordination of presynaptic and postsynaptic activity induces timing-dependent hippocampal synaptic plasticity. *J. Neurosci.*, **2012**, *32*(36), 12337-12348.

[39] Buchanan, K.A.; Petrovic, M.M.; Chamberlain, S.E.; Marrion, N.V.; Mellor, J.R. Facilitation of long-term potentiation by muscarinic M(1) receptors is mediated by inhibition of SK channels. *Neuron*, **2010**, *68*(5), 948-963.

[40] Dickinson, B.A.; Jo, J.; Seok, H.; Son, G.H.; Whitcomb, D.J.; Davies, C.H.; Sheng, M.; Collingridge, G.L.; Cho, K. A novel mechanism of hippocampal LTD involving muscarinic receptor-triggered interactions between AMPARs, GRIP and liprin-alpha. *Mol. Brain*, **2009**, *2*, 18.

[41] Caruana, D.A.; Warburton, E.C.; Bashir, Z.I. Induction of activity-dependent LTD requires muscarinic receptor activation in medial prefrontal cortex. *J. Neurosci.*, **2011**, *31*(50), 18464-18478.

[42] McCutchen, E.; Scheiderer, C.L.; Dobrunz, L.E.; McMahon, L.L. Coexistence of muscarinic long-term depression with electrically induced long-term potentiation and depression at CA3-CA1 synapses. *J. Neurophysiol.*, **2006**, *96*(6), 3114-3121.

[43] Lane, R.M.; Potkin, S.G.; Enz, A. Targeting acetylcholinesterase and butyrylcholinesterase in dementia. *Int. J. Neuropsychopharmacol.*, **2006**, *9*(1), 101-124.

[44] Birks, J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane. Database. Syst. Rev.*, **2006**(1), CD005593.

[45] Mohamed, T.; Rao, P.P. Alzheimer's disease: emerging trends in small molecule therapies. *Curr. Med. Chem.*, **2011**, *18*(28), 4299-4320.

[46] Pepeu, G.; Giovannini, M.G. Cholinesterase inhibitors and beyond. *Curr. Alzheimer Res.*, **2009**, *6*(2), 86-96.

[47] Ibach, B.; Haen, E. Acetylcholinesterase inhibition in Alzheimer's Disease. *Curr. Pharm. Des*, **2004**, *10*(3), 231-251.

[48] Fisher, A. Cholinergic treatments with emphasis on m1 muscarinic agonists as potential disease-modifying agents for Alzheimer's disease. *Neurotherapeutics.*, **2008**, *5*(3), 433-442.

[49] Caccamo, A.; Fisher, A.; LaFerla, F.M. M1 agonists as a potential disease-modifying therapy for Alzheimer's disease. *Curr. Alzheimer Res.*, **2009**, *6*(2), 112-117.

[50] Parri, H.R.; Hernandez, C.M.; Dineley, K.T. Research update: Alpha7 nicotinic acetylcholine receptor mechanisms in Alzheimer's disease. *Biochem. Pharmacol.*, **2011**, *82*(8), 931-942.

[51] Wallace, T.L.; Porter, R.H. Targeting the nicotinic alpha7 acetylcholine receptor to enhance cognition in disease. *Biochem. Pharmacol.*, **2011**, *82*(8), 891-903.

[52] Hernandez, C.M.; Dineley, K.T. alpha7 nicotinic acetylcholine receptors in Alzheimer's disease: neuroprotective, neurotrophic or both? *Curr. Drug Targets.*, **2012**, *13*(5), 613-622.

[53] Resende, R.R.; Adhikari, A. Cholinergic receptor pathways involved in apoptosis, cell proliferation and neuronal differentiation. *Cell Commun. Signal.*, **2009**, *7*, 20.

[54] Rimmaudo, L.E.; de la Torre, E.; Sacerdote de, L.E.; Sales, M.E. Muscarinic receptors are involved in LMM3 tumor cells proliferation and angiogenesis. *Biochem. Biophys. Res. Commun.*, **2005**, *334*(4), 1359-1364.

[55] Ma, W.; Li, B.S.; Zhang, L.; Pant, H.C. Signaling cascades implicated in muscarinic regulation of proliferation of neural stem and progenitor cells. *Drug News Perspect.*, **2004**, *17*(4), 258-266.

[56] Itou, Y.; Nochi, R.; Kuribayashi, H.; Saito, Y.; Hisatsune, T. Cholinergic activation of hippocampal neural stem cells in aged dentate gyrus. *Hippocampus*, **2011**, *21*(4), 446-459.

[57] Lanzafame, A.A.; Christopoulos, A.; Mitchelson, F. Cellular signaling mechanisms for muscarinic acetylcholine receptors. *Receptors. Channels*, **2003**, *9*(4), 241-260.

[58] Leloup, C.; Michaelson, D.M.; Fisher, A.; Hartmann, T.; Beyreuther, K.; Stein, R. M1 muscarinic receptors block caspase

activation by phosphoinositide 3-kinase- and MAPK/ERK-independent pathways. *Cell Death. Differ.*, **2000**, *7*(9), 825-833.

[59] De, S.P.; Shestopal, S.A.; King, T.D.; Zmijewska, A.; Song, L.; Jope, R.S. Muscarinic receptor activation protects cells from apoptotic effects of DNA damage, oxidative stress, and mitochondrial inhibition. *J. Biol. Chem.*, **2003**, *278*(13), 11086-11093.

[60] Budd, D.C.; Spragg, E.J.; Ridd, K.; Tobin, A.B. Signalling of the M3-muscarinic receptor to the anti-apoptotic pathway. *Biochem. J.*, **2004**, *381*(Pt 1), 43-49.

[61] Yan, G.M.; Lin, S.Z.; Irwin, R.P.; Paul, S.M. Activation of muscarinic cholinergic receptors blocks apoptosis of cultured cerebellar granule neurons. *Mol. Pharmacol.*, **1995**, *47*(2), 248-257.

[62] Hui, Y.; Zhao, Y.; Ma, N.; Peng, Y.; Pan, Z.; Zou, C.; Zhang, P.; Du, Z. M3-mAChR stimulation exerts anti-apoptotic effect via activating the HIF-1alpha/HO-1/VEGF signaling pathway in H9c2 rat ventricular cells. *J. Cardiovasc. Pharmacol.*, **2012**, *60*(5), 474-482.

[63] Li, B.S.; Ma, W.; Zhang, L.; Barker, J.L.; Stenger, D.A.; Pant, H.C. Activation of phosphatidylinositol-3 kinase (PI-3K) and extracellular regulated kinases (Erk1/2) is involved in muscarinic receptor-mediated DNA synthesis in neural progenitor cells. *J. Neurosci.*, **2001**, *21*(5), 1569-1579.

[64] Almasieh, M.; Zhou, Y.; Kelly, M.E.; Casanova, C.; Di, P.A. Structural and functional neuroprotection in glaucoma: role of galantamine-mediated activation of muscarinic acetylcholine receptors. *Cell Death. Dis.*, **2010**, *1*, e27.

[65] Zhu, X.; Zhou, W.; Cui, Y.; Zhu, L.; Li, J.; Feng, X.; Shao, B.; Qi, H.; Zheng, J.; Wang, H.; Chen, H. Pilocarpine protects cobalt chloride-induced apoptosis of RGC-5 cells: involvement of muscarinic receptors and HIF-1 alpha pathway. *Cell Mol. Neurobiol.*, **2010**, *30*(3), 427-435.

[66] Marte, B.M.; Downward, J. PKB/Akt: connecting phosphoinositide 3-kinase to cell survival and beyond. *Trends Biochem. Sci.*, **1997**, *22*(9), 355-358.

[67] Dudek, H.; Datta, S.R.; Franke, T.F.; Birnbaum, M.J.; Yao, R.; Cooper, G.M.; Segal, R.A.; Kaplan, D.R.; Greenberg, M.E. Regulation of neuronal survival by the serine-threonine protein kinase Akt. *Science*, **1997**, *275*(5300), 661-665.

[68] Kulik, G.; Klippel, A.; Weber, M.J. Antiapoptotic signalling by the insulin-like growth factor I receptor, phosphatidylinositol 3-kinase, and Akt. *Mol. Cell Biol.*, **1997**, *17*(3), 1595-1606.

[69] Budd, D.C.; McDonald, J.; Emsley, N.; Cain, K.; Tobin, A.B. The C-terminal tail of the M3-muscarinic receptor possesses anti-apoptotic properties. *J. Biol. Chem.*, **2003**, *278*(21), 19565-19573.

[70] Navakkode, S.; Korte, M. Cooperation between cholinergic and glutamatergic receptors are essential to induce BDNF-dependent long-lasting memory storage. *Hippocampus*, **2012**, *22*(2), 335-346.

[71] French, S.J.; Humby, T.; Horner, C.H.; Sofroniew, M.V.; Rattray, M. Hippocampal neurotrophin and trk receptor mRNA levels are altered by local administration of nicotine, carbachol and pilocarpine. *Brain Res. Mol. Brain Res.*, **1999**, *67*(1), 124-136.

[72] Lindholm, D.; da Penha, B.M.; Cooper, J.; Thoenen, H.; Castren, E. Brain-derived neurotrophic factor and neurotrophin-4 increase neurotrophin-3 expression in the rat hippocampus. *Int. J. Dev. Neurosci.*, **1994**, *12*(8), 745-751.

[73] Mudo, G.; Jiang, X.H.; Timmusk, T.; Bindoni, M.; Belluardo, N. Change in neurotrophins and their receptor mRNAs in the rat forebrain after status epilepticus induced by pilocarpine. *Epilepsia*, **1996**, *37*(2), 198-207.

[74] Wu, J.; Lukas, R.J. Naturally-expressed nicotinic acetylcholine receptor subtypes. *Biochem. Pharmacol.*, **2011**, *82*(8), 800-807.

[75] Whiteaker, P.; Davies, A.R.; Marks, M.J.; Blagbrough, I.S.; Potter, B.V.; Wolstenholme, A.J.; Collins, A.C.; Wonnacott, S. An autoradiographic study of the distribution of binding sites for the novel alpha7-selective nicotinic radioligand [3H]-methyllycaconitine in the mouse brain. *Eur. J. Neurosci.*, **1999**, *11*(8), 2689-2696.

[76] Wonnacott, S. Presynaptic nicotinic ACh receptors. *Trends Neurosci.*, **1997**, *20* (2), 92-98.

[77] Fujii, S.; Ji, Z.; Morita, N.; Sumikawa, K. Acute and chronic nicotine exposure differentially facilitate the induction of LTP. *Brain Res.*, **1999**, *846*(1), 137-143.

[78] Mann, E.O.; Greenfield, S.A. Novel modulatory mechanisms revealed by the sustained application of nicotine in the guinea-pig hippocampus *in vitro*. *J. Physiol*, **2003**, *551*(Pt 2), 539-550.

[79] Ji, D.; Lape, R.; Dani, J.A. Timing and location of nicotinic activity enhances or depresses hippocampal synaptic plasticity. *Neuron*, **2001**, *31*(1), 131-141.

[80] Sharma, G.; Vijayaraghavan, S. Modulation of presynaptic store calcium induces release of glutamate and postsynaptic firing. *Neuron*, **2003**, *38*(6), 929-939.

[81] Welsby, P.J.; Rowan, M.J.; Anwyl, R. Intracellular mechanisms underlying the nicotinic enhancement of LTP in the rat dentate gyrus. *Eur. J. Neurosci.*, **2009**, *29*(1), 65-75.

[82] Tu, B.; Gu, Z.; Shen, J.X.; Lamb, P.W.; Yakel, J.L. Characterization of a nicotine-sensitive neuronal population in rat entorhinal cortex. *J. Neurosci.*, **2009**, *29*(33), 10436-10448.

[83] Gotti, C.; Clementi, F. Neuronal nicotinic receptors: from structure to pathology. *Prog. Neurobiol.*, **2004**, *74*(6), 363-396.

[84] Mudo, G.; Belluardo, N.; Fuxe, K. Nicotinic receptor agonists as neuroprotective/neurotrophic drugs. Progress in molecular mechanisms. *J. Neural Transm.*, **2007**, *114*(1), 135-147.

[85] Shaw, S.; Bencherif, M.; Marrero, M.B. Janus kinase 2, an early target of alpha 7 nicotinic acetylcholine receptor-mediated neuroprotection against Abeta-(1-42) amyloid. *J. Biol. Chem.*, **2002**, *277*(47), 44920-44924.

[86] Kihara, T.; Shimohama, S.; Sawada, H.; Honda, K.; Nakamizo, T.; Shibasaki, H.; Kume, T.; Akaike, A. alpha 7 nicotinic receptor transduces signals to phosphatidylinositol 3-kinase to block A beta-amyloid-induced neurotoxicity. *J. Biol. Chem.*, **2001**, *276*(17), 13541-13546.

[87] Liu, Y.; Hu, J.; Wu, J.; Zhu, C.; Hui, Y.; Han, Y.; Huang, Z.; Ellsworth, K.; Fan, W. alpha7 nicotinic acetylcholine receptor-mediated neuroprotection against dopaminergic neuron loss in an MPTP mouse model via inhibition of astrocyte activation. *J. Neuroinflammation.*, **2012**, *9*, 98.

[88] Hejmadi, M.V.; Dajas-Bailador, F.; Barns, S.M.; Jones, B.; Wonnacott, S. Neuroprotection by nicotine against hypoxia-induced apoptosis in cortical cultures involves activation of multiple nicotinic acetylcholine receptor subtypes. *Mol. Cell Neurosci.*, **2003**, *24*(3), 779-786.

[89] Ueda, M.; Iida, Y.; Kitamura, Y.; Kawashima, H.; Ogawa, M.; Magata, Y.; Saji, H. 5-Iodo-A-85380, a specific ligand for alpha 4 beta 2 nicotinic acetylcholine receptors, prevents glutamate neurotoxicity in rat cortical cultured neurons. *Brain Res.*, **2008**, *1199*, 46-52.

[90] Orr-Urtreger, A.; Broide, R.S.; Kasten, M.R.; Dang, H.; Dani, J.A.; Beaudet, A.L.; Patrick, J.W. Mice homozygous for the L250T mutation in the alpha7 nicotinic acetylcholine receptor show increased neuronal apoptosis and die within 1 day of birth. *J. Neurochem.*, **2000**, *74*(5), 2154-2166.

[91] Nanri, M.; Yamamoto, J.; Miyake, H.; Watanabe, H. Protective effect of GTS-21, a novel nicotinic receptor agonist, on delayed neuronal death induced by ischemia in gerbils. *Jpn. J. Pharmacol.*, **1998**, *76*(1), 23-29.

[92] Martin, L.F.; Kem, W.R.; Freedman, R. Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. *Psychopharmacology (Berl)*, **2004**, *174*(1), 54-64.

[93] Zeidler, R.; Albermann, K.; Lang, S. Nicotine and apoptosis. *Apoptosis.*, **2007**, *12*(11), 1927-1943.

[94] Mai, H.; May, W.S.; Gao, F.; Jin, Z.; Deng, X. A functional role for nicotine in Bcl2 phosphorylation and suppression of apoptosis. *J. Biol. Chem.*, **2003**, *278*(3), 1886-1891.

[95] Finkbeiner, S. CREB couples neurotrophin signals to survival messages. *Neuron*, **2000**, *25*(1), 11-14.

[96] Mazzucchelli, C.; Brambilla, R. Ras-related and MAPK signalling in neuronal plasticity and memory formation. *Cell Mol. Life Sci.*, **2000**, *57*(4), 604-611.

[97] Zhu, Y.; Culmsee, C.; Klumpp, S.; Krieglstein, J. Neuroprotection by transforming growth factor-beta1 involves activation of nuclear factor-kappaB through phosphatidylinositol-3-OH kinase/Akt and mitogen-activated protein kinase-extracellular-signal regulated kinase1,2 signaling pathways. *Neuroscience*, **2004**, *123*(4), 897-906.

[98] Belluardo, N.; Mudo, G.; Blum, M.; Itoh, N.; Agnati, L.; Fuxe, K. Nicotine-induced FGF-2 mRNA in rat brain is preserved during aging. *Neurobiol. Aging*, **2004**, *25*(10), 1333-1342.

[99] Kita, Y.; Ago, Y.; Takano, E.; Fukada, A.; Takuma, K.; Matsuda, T. Galantamine increases hippocampal insulin-like growth factor 2 expression via alpha7 nicotinic acetylcholine receptors in mice. *Psychopharmacology (Berl)*, **2013**, *225*(3), 543-551.

[100] Frinchi, M.; Di, L., V; Olivieri, M.; Fuxe, K.; Belluardo, N.; Mudo, G. FGF-2/FGFR1 neurotrophic system expression level and its basal activation do not account for the age-dependent decline of precursor cell proliferation in the subventricular zone of rat brain. *Brain Res.*, **2010**, *1358*, 39-45.

[101] Mudo, G.; Belluardo, N.; Mauro, A.; Fuxe, K. Acute intermittent nicotine treatment induces fibroblast growth factor-2 in the subventricular zone of the adult rat brain and enhances neuronal precursor cell proliferation. *Neuroscience*, **2007**, *145*(2), 470-483.

[102] Mudo, G.; Bonomo, A.; Di, L., V; Frinchi, M.; Fuxe, K.; Belluardo, N. The FGF-2/FGFRs neurotrophic system promotes neurogenesis in the adult brain. *J. Neural Transm.*, **2009**, *116*(8), 995-1005.

[103] Takarada, T.; Nakamichi, N.; Kitajima, S.; Fukumori, R.; Nakazato, R.; Le, N.Q.; Kim, Y.H.; Fujikawa, K.; Kou, M.; Yoneda, Y. Promoted neuronal differentiation after activation of alpha4/beta2 nicotinic acetylcholine receptors in undifferentiated neural progenitors. *PLoS One*, **2012**, *7*(10), e46177.

[104] Ishizuka, T.; Goshima, H.; Ozawa, A.; Watanabe, Y. Effect of nicotine on the proliferation and differentiation of mouse induced pluripotent stem cells. *Curr. Med. Chem.*, **2012**, *19*(30), 5164-5169.

[105] Dasgupta, P.; Chellappan, S.P. Nicotine-mediated cell proliferation and angiogenesis: new twists to an old story. *Cell Cycle*, **2006**, *5*(20), 2324-2328.

[106] Harrist, A.; Beech, R.D.; King, S.L.; Zanardi, A.; Cleary, M.A.; Caldarone, B.J.; Eisch, A.; Zoli, M.; Picciotto, M.R. Alteration of hippocampal cell proliferation in mice lacking the beta 2 subunit of the neuronal nicotinic acetylcholine receptor. *Synapse*, **2004**, *54*(4), 200-206.

[107] Sharma, G.; Vijayaraghavan, S. Nicotinic receptor signaling in nonexcitable cells. *J. Neurobiol.*, **2002**, *53*(4), 524-534.

[108] Lowes, V.L.; Ip, N.Y.; Wong, Y.H. Integration of signals from receptor tyrosine kinases and g protein-coupled receptors. *Neurosignals.*, **2002**, *11*(1), 5-19.

[109] Shah, B.H.; Catt, K.J. GPCR-mediated transactivation of RTKs in the CNS: mechanisms and consequences. *Trends Neurosci.*, **2004**, *27*(1), 48-53.

[110] Liebmann, C. EGF receptor activation by GPCRs: an universal pathway reveals different versions. *Mol. Cell Endocrinol.*, **2011**, *331*(2), 222-231.

[111] Waters, C.; Pyne, S.; Pyne, N.J. The role of G-protein coupled receptors and associated proteins in receptor tyrosine kinase signal transduction. *Semin. Cell Dev. Biol.*, **2004**, *15*(3), 309-323.

[112] Delcourt, N.; Bockaert, J.; Marin, P. GPCR-jacking: from a new route in RTK signalling to a new concept in GPCR activation. *Trends Pharmacol. Sci.*, **2007**, *28*(12), 602-607.

[113] Little, P.J.; Burch, M.L.; Al-aryahi, S.; Zheng, W. The paradigm of G protein receptor transactivation: a mechanistic definition and novel example. *Scientific World J.*, **2011**, *11*, 709-714.

[114] Luttrell, L.M.; van, B.T.; Hawes, B.E.; Koch, W.J.; Touhara, K.; Lefkowitz, R.J. G beta gamma subunits mediate mitogen-activated protein kinase activation by the tyrosine kinase insulin-like growth factor 1 receptor. *J. Biol. Chem.*, **1995**, *270*(28), 16495-16498.

[115] Povsic, T.J.; Kohout, T.A.; Lefkowitz, R.J. Beta-arrestin1 mediates insulin-like growth factor 1 (IGF-1) activation of phosphatidylinositol 3-kinase (PI3K) and anti-apoptosis. *J. Biol. Chem.*, **2003**, *278*(51), 51334-51339.

[116] Natarajan, K.; Berk, B.C. Crosstalk coregulation mechanisms of G protein-coupled receptors and receptor tyrosine kinases. *Methods Mol. Biol.*, **2006**, *332*, 51-77.

[117] Roudabush, F.L.; Pierce, K.L.; Maudsley, S.; Khan, K.D.; Luttrell, L.M. Transactivation of the EGF receptor mediates IGF-1-stimulated shc phosphorylation and ERK1/2 activation in COS-7 cells. *J. Biol. Chem.*, **2000**, *275*(29), 22583-22589.

[118] Gilmore, A.P.; Valentijn, A.J.; Wang, P.; Ranger, A.M.; Bundred, N.; O'Hare, M.J.; Wakeling, A.; Korsmeyer, S.J.; Streuli, C.H. Activation of BAD by therapeutic inhibition of epidermal growth factor receptor and transactivation by insulin-like growth factor receptor. *J. Biol. Chem.*, **2002**, *277*(31), 27643-27650.

[119] Daub, H.; Wallasch, C.; Lankenau, A.; Herrlich, A.; Ullrich, A. Signal characteristics of G protein-transactivated EGF receptor. *EMBO J.*, **1997**, *16*(23), 7032-7044.

[120] Daub, H.; Weiss, F.U.; Wallasch, C.; Ullrich, A. Role of transactivation of the EGF receptor in signalling by G-protein-coupled receptors. *Nature*, **1996**, *379*(6565), 557-560.

[121] Ohtsu, H.; Dempsey, P.J.; Eguchi, S. ADAMs as mediators of EGF receptor transactivation by G protein-coupled receptors. *Am. J. Physiol Cell Physiol*, **2006**, *291*(1), C1-10.

[122] Prenzel, N.; Zwick, E.; Daub, H.; Leserer, M.; Abraham, R.; Wallasch, C.; Ullrich, A. EGF receptor transactivation by G-protein-coupled receptors requires metalloproteinase cleavage of proHB-EGF. *Nature*, **1999**, *402*(6764), 884-888.

[123] Borroto-Escuela, D.O.; Romero-Fernandez, W.; Mudo, G.; Perez-Alea, M.; Ciruela, F.; Tarakanov, A.O.; Narvaez, M.; Di, L., V; Agnati, L.F.; Belluardo, N.; Fuxe, K. Fibroblast growth factor receptor 1- 5-hydroxytryptamine 1A heteroreceptor complexes and their enhancement of hippocampal plasticity. *Biol. Psychiatry*, **2012**, *71*(1), 84-91.

[124] Pyne, N.J.; Waters, C.M.; Long, J.S.; Moughal, N.A.; Tigyi, G.; Pyne, S. Receptor tyrosine kinase-G-protein coupled receptor complex signaling in mammalian cells. *Adv. Enzyme Regul.*, **2007**, *47*, 271-280.

[125] Werry, T.D.; Sexton, P.M.; Christopoulos, A. "Ins and outs" of seven-transmembrane receptor signalling to ERK. *Trends Endocrinol. Metab.*, **2005**, *16*(1), 26-33.

[126] Wetzker, R.; Bohmer, F.D. Transactivation joins multiple tracks to the ERK/MAPK cascade. *Nat. Rev. Mol. Cell Biol.*, **2003**, *4*(8), 651-657.

[127] Drube, S.; Stirnweiss, J.; Valkova, C.; Liebmann, C. Ligand-independent and EGF receptor-supported transactivation: lessons from beta2-adrenergic receptor signalling. *Cell Signal.*, **2006**, *18*(10), 1633-1646.

[128] Biscardi, J.S.; Ishizawar, R.C.; Silva, C.M.; Parsons, S.J. Tyrosine kinase signalling in breast cancer: epidermal growth factor receptor and c-Src interactions in breast cancer. *Breast Cancer Res.*, **2000**, *2*(3), 203-210.

[129] Lee, F.S.; Rajagopal, R.; Kim, A.H.; Chang, P.C.; Chao, M.V. Activation of Trk neurotrophin receptor signaling by pituitary adenylate cyclase-activating polypeptides. *J. Biol. Chem.*, **2002**, *277*(11), 9096-9102.

[130] Lin, X.; Li, X.; Jiang, M.; Chen, L.; Xu, C.; Zhang, W.; Zhao, H.; Sun, B.; Xu, X.; Nan, F.; Liu, J. An activity-based probe reveals dynamic protein-protein interactions mediating IGF-1R transactivation by the GABA(B) receptor. *Biochem. J.*, **2012**, *443*(3), 627-634.

[131] Flajolet, M.; Wang, Z.; Futter, M.; Shen, W.; Nuangchamnong, N.; Bendor, J.; Wallach, I.; Nairn, A.C.; Surmeier, D.J.; Greengard, P. FGF acts as a co-transmitter through adenosine A(2A) receptor to regulate synaptic plasticity. *Nat. Neurosci.*, **2008**, *11*(12), 1402-1409.

[132] Huang, Y.Z.; McNamara, J.O. Neuroprotective effects of reactive oxygen species mediated by BDNF-independent activation of TrkB. *J. Neurosci.*, **2012**, *32*(44), 15521-15532.

[133] Huang, Y.Z.; Pan, E.; Xiong, Z.Q.; McNamara, J.O. Zinc-mediated transactivation of TrkB potentiates the hippocampal mossy fiber-CA3 pyramid synapse. *Neuron*, **2008**, *57*(4), 546-558.

[134] Burch, M.L.; Osman, N.; Getachew, R.; Al-aryahi, S.; Poronnik, P.; Zheng, W.; Hill, M.A.; Little, P.J. G protein coupled receptor transactivation: extending the paradigm to include serine/threonine kinase receptors. *Int. J. Biochem. Cell Biol.*, **2012**, *44*(5), 722-727.

[135] Little, P.J.; Burch, M.L.; Getachew, R.; Al-aryahi, S.; Osman, N. Endothelin-1 stimulation of proteoglycan synthesis in vascular smooth muscle is mediated by endothelin receptor transactivation of the transforming growth factor-[beta] type I receptor. *J. Cardiovasc. Pharmacol.*, **2010**, *56*(4), 360-368.

[136] Jorissen, R.N.; Walker, F.; Pouliot, N.; Garrett, T.P.; Ward, C.W.; Burgess, A.W. Epidermal growth factor receptor: mechanisms of activation and signalling. *Exp. Cell Res.*, **2003**, *284*(1), 31-53.

[137] Asakura, M.; Kitakaze, M.; Takashima, S.; Liao, Y.; Ishikura, F.; Yoshinaka, T.; Ohmoto, H.; Node, K.; Yoshino, K.; Ishiguro, H.; Asanuma, H.; Sanada, S.; Matsumura, Y.; Takeda, H.; Beppu, S.; Tada, M.; Hori, M.; Higashiyama, S. Cardiac hypertrophy is inhibited by antagonism of ADAM12 processing of HB-EGF: metalloproteinase inhibitors as a new therapy. *Nat. Med.*, **2002**, *8*(1), 35-40.

[138] Cheng, C.Y.; Tseng, H.C.; Yang, C.M. Bradykinin-mediated cell proliferation depends on transactivation of EGF receptor in corneal fibroblasts. *J. Cell Physiol*, **2012**, *227*(4), 1367-1381.

[139] Yan, Y.; Shirakabe, K.; Werb, Z. The metalloprotease Kuzbanian (ADAM10) mediates the transactivation of EGF receptor by G protein-coupled receptors. *J. Cell Biol.*, **2002**, *158*(2), 221-226.

[140] Moody, T.W.; Sancho, V.; di, F.A.; Nuche-Berenguer, B.; Mantey, S.; Jensen, R.T. Bombesin receptor subtype-3 agonists stimulate the growth of lung cancer cells and increase EGF receptor tyrosine phosphorylation. *Peptides*, **2011**, *32*(8), 1677-1684.

[141] McElroy, S.J.; Hobbs, S.; Kallen, M.; Tejera, N.; Rosen, M.J.; Grishin, A.; Matta, P.; Schneider, C.; Upperman, J.; Ford, H.; Polk, D.B.; Weitkamp, J.H. Transactivation of EGFR by LPS induces COX-2 expression in enterocytes. *PLoS One*, **2012**, *7*(5), e38373.

[142] Hsu, D.; Fukata, M.; Hernandez, Y.G.; Sotolongo, J.P.; Goo, T.; Maki, J.; Hayes, L.A.; Ungaro, R.C.; Chen, A.; Breglio, K.J.; Xu, R.; Abreu, M.T. Toll-like receptor 4 differentially regulates epidermal growth factor-related growth factors in response to intestinal mucosal injury. *Lab. Invest.*, **2010**, *90*(9), 1295-1305.

[143] Prevot, V.; Cornea, A.; Mungenast, A.; Smiley, G.; Ojeda, S.R. Activation of erbB-1 signaling in tanycytes of the median eminence stimulates transforming growth factor beta1 release via prostaglandin E2 production and induces cell plasticity. *J. Neurosci.*, **2003**, *23*(33), 10622-10632.

[144] Cussac, D.; Schaak, S.; Denis, C.; Paris, H. alpha 2B-adrenergic receptor activates MAPK via a pathway involving arachidonic acid metabolism, matrix metalloproteinases, and epidermal growth factor receptor transactivation. *J. Biol. Chem.*, **2002**, *277*(22), 19882-19888.

[145] Xie, K.Q.; Zhang, L.M.; Cao, Y.; Zhu, J.; Feng, L.Y. Adenosine A(1) receptor-mediated transactivation of the EGF receptor produces a neuroprotective effect on cortical neurons *in vitro*. *Acta Pharmacol. Sin.*, **2009**, *30*(7), 889-898.

[146] Milenkovic, I.; Weick, M.; Wiedemann, P.; Reichenbach, A.; Bringmann, A. P2Y receptor-mediated stimulation of Muller glial cell DNA synthesis: dependence on EGF and PDGF receptor transactivation. *Invest Ophthalmol. Vis. Sci.*, **2003**, *44*(3), 1211-1220.

[147] Li, B.; Zhang, S.; Zhang, H.; Nu, W.; Cai, L.; Hertz, L.; Peng, L. Fluoxetine-mediated 5-HT2B receptor stimulation in astrocytes causes EGF receptor transactivation and ERK phosphorylation. *Psychopharmacology (Berl)*, **2008**, *201*(3), 443-458.

[148] Peavy, R.D.; Chang, M.S.; Sanders-Bush, E.; Conn, P.J. Metabotropic glutamate receptor 5-induced phosphorylation of extracellular signal-regulated kinase in astrocytes depends on transactivation of the epidermal growth factor receptor. *J. Neurosci.*, **2001**, *21*(24), 9619-9628.

[149] Heldin, C.H.; Westermark, B. Mechanism of action and *in vivo* role of platelet-derived growth factor. *Physiol Rev.*, **1999**, *79*(4), 1283-1316.

[150] Liu, Y.; Li, M.; Warburton, R.R.; Hill, N.S.; Fanburg, B.L. The 5-HT transporter transactivates the PDGFbeta receptor in pulmonary artery smooth muscle cells. *FASEB J.*, **2007**, *21*(11), 2725-2734.

[151] Nebigil, C.G.; Launay, J.M.; Hickel, P.; Tournois, C.; Maroteaux, L. 5-hydroxytryptamine 2B receptor regulates cell-cycle progression: cross-talk with tyrosine kinase pathways. *Proc. Natl. Acad. Sci. U. S. A*, **2000**, *97*(6), 2591-2596.

[152] Kruk, J.S.; Vasefi, M.S.; Liu, H.; Heikkila, J.J.; Beazely, M.A. 5-HT(1A) receptors transactivate the platelet-derived growth factor receptor type beta in neuronal cells. *Cell Signal.*, **2013**, *25*(1), 133-143.

[153] Oak, J.N.; Lavine, N.; Van Tol, H.H. Dopamine D(4) and D(2L) Receptor Stimulation of the Mitogen-Activated Protein Kinase Pathway Is Dependent on trans-Activation of the Platelet-Derived Growth Factor Receptor. *Mol. Pharmacol.*, **2001**, *60*(1), 92-103.

[154] Kotecha, S.A.; Oak, J.N.; Jackson, M.F.; Perez, Y.; Orser, B.A.; Van Tol, H.H.; MacDonald, J.F. A D2 class dopamine receptor transactivates a receptor tyrosine kinase to inhibit NMDA receptor transmission. *Neuron*, **2002**, *35*(6), 1111-1122.

[155] Heeneman, S.; Haendeler, J.; Saito, Y.; Ishida, M.; Berk, B.C. Angiotensin II induces transactivation of two different populations of the platelet-derived growth factor beta receptor. Key role for the p66 adaptor protein Shc. *J. Biol. Chem.*, **2000**, *275*(21), 15926-15932.

[156] Wang, C.; Wu, L.L.; Liu, J.; Zhang, Z.G.; Fan, D.; Li, L. Crosstalk between angiotensin II and platelet derived growth factor-BB mediated signal pathways in cardiomyocytes. *Chin Med. J. (Engl. )*, **2008**, *121*(3), 236-240.

[157] Tanimoto, T.; Lungu, A.O.; Berk, B.C. Sphingosine 1-phosphate transactivates the platelet-derived growth factor beta receptor and epidermal growth factor receptor in vascular smooth muscle cells. *Circ. Res.*, **2004**, *94*(8), 1050-1058.

[158] Goppelt-Struebe, M.; Fickel, S.; Reiser, C.O. The platelet-derived-growth-factor receptor, not the epidermal-growth-factor receptor, is used by lysophosphatidic acid to activate p42/44 mitogen-activated protein kinase and to induce prostaglandin G/H synthase-2 in mesangial cells. *Biochem. J.*, **2000**, *345*(Pt 2 ), 217-224.

[159] Wang, L.; Cummings, R.; Zhao, Y.; Kazlauskas, A.; Sham, J.K.; Morris, A.; Georas, S.; Brindley, D.N.; Natarajan, V. Involvement of phospholipase D2 in lysophosphatidate-induced transactivation of platelet-derived growth factor receptor-beta in human bronchial epithelial cells. *J. Biol. Chem.*, **2003**, *278*(41), 39931-39940.

[160] McMahon, B.; Mitchell, D.; Shattock, R.; Martin, F.; Brady, H.R.; Godson, C. Lipoxin, leukotriene, and PDGF receptors cross-talk to regulate mesangial cell proliferation. *FASEB J.*, **2002**, *16*(13), 1817-1819.

[161] Cheng, H.L.; Steinway, M.; Delaney, C.L.; Franke, T.F.; Feldman, E.L. IGF-I promotes Schwann cell motility and survival via activation of Akt. *Mol. Cell Endocrinol.*, **2000**, *170*(1-2), 211-215.

[162] Carro, E.; Trejo, J.L.; Nunez, A.; Torres-Aleman, I. Brain repair and neuroprotection by serum insulin-like growth factor I. *Mol. Neurobiol.*, **2003**, *27*(2), 153-162.

[163] Delcourt, N.; Thouvenot, E.; Chanrion, B.; Galeotti, N.; Jouin, P.; Bockaert, J.; Marin, P. PACAP type I receptor transactivation is essential for IGF-1 receptor signalling and antiapoptotic activity in neurons. *EMBO J.*, **2007**, *26*(6), 1542-1551.

[164] Tu, H.; Xu, C.; Zhang, W.; Liu, Q.; Rondard, P.; Pin, J.P.; Liu, J. GABAB receptor activation protects neurons from apoptosis via IGF-1 receptor transactivation. *J. Neurosci.*, **2010**, *30*(2), 749-759.

[165] Skaper, S.D. The neurotrophin family of neurotrophic factors: an overview. *Methods Mol. Biol.*, **2012**, *846*, 1-12.

[166] Arevalo, J.C.; Wu, S.H. Neurotrophin signaling: many exciting surprises! *Cell Mol. Life Sci.*, **2006**, *63*(13), 1523-1537.

[167] Rantamaki, T.; Vesa, L.; Antila, H.; Di, L.A.; Tammela, P.; Schmitt, A.; Lesch, K.P.; Rios, M.; Castren, E. Antidepressant drugs transactivate TrkB neurotrophin receptors in the adult rodent brain independently of BDNF and monoamine transporter blockade. *PLoS One*, **2011**, *6*(6), e20567.

[168] Rantamaki, T.; Hendolin, P.; Kankaanpaa, A.; Mijatovic, J.; Piepponen, P.; Domenici, E.; Chao, M.V.; Mannisto, P.T.; Castren, E. Pharmacologically diverse antidepressants rapidly activate brain-derived neurotrophic factor receptor TrkB and induce phospholipase-Cgamma signaling pathways in mouse brain. *Neuropsychopharmacology*, **2007**, *32*(10), 2152-2162.

[169] Rantamaki, T.; Castren, E. Targeting TrkB neurotrophin receptor to treat depression. *Expert. Opin. Ther. Targets.*, **2008**, *12*(6), 705-715.

[170] Sairanen, M.; Lucas, G.; Ernfors, P.; Castren, M.; Castren, E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. *J. Neurosci.*, **2005**, *25*(5), 1089-1094.

[171] Saarelainen, T.; Hendolin, P.; Lucas, G.; Koponen, E.; Sairanen, M.; MacDonald, E.; Agerman, K.; Haapasalo, A.; Nawa, H.; Aloyz, R.; Ernfors, P.; Castren, E. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J. Neurosci.*, **2003**, *23*(1), 349-357.

[172] Lee, F.S.; Chao, M.V. Activation of Trk neurotrophin receptors in the absence of neurotrophins. *Proc. Natl. Acad. Sci. U. S. A*, **2001**, *98*(6), 3555-3560.

[173] Rajagopal, R.; Chao, M.V. A role for Fyn in Trk receptor transactivation by G-protein-coupled receptor signaling. *Mol. Cell Neurosci.*, **2006**, *33*(1), 36-46.

[174] Shi, G.X.; Jin, L.; Andres, D.A. Src-dependent TrkA transactivation is required for pituitary adenylate cyclase-activating polypeptide 38-mediated Rit activation and neuronal differentiation. *Mol. Biol. Cell*, **2010**, *21*(9), 1597-1608.

[175] Wiese, S.; Jablonka, S.; Holtmann, B.; Orel, N.; Rajagopal, R.; Chao, M.V.; Sendtner, M. Adenosine receptor A2A-R contributes to motoneuron survival by transactivating the tyrosine kinase receptor TrkB. *Proc. Natl. Acad. Sci. U. S. A*, **2007**, *104*(43), 17210-17215.

[176] Swift, J.L.; Godin, A.G.; Dore, K.; Freland, L.; Bouchard, N.; Nimmo, C.; Sergeev, M.; De, K.Y.; Wiseman, P.W.; Beaulieu, J.M. Quantification of receptor tyrosine kinase transactivation through direct dimerization and surface density measurements in single cells. *Proc. Natl. Acad. Sci. U. S. A*, **2011**, *108*(17), 7016-7021.

[177] Beaulieu, J.M.; Gainetdinov, R.R. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol. Rev.*, **2011**, *63*(1), 182-217.

[178] Vaccarino, F.M.; Schwartz, M.L.; Raballo, R.; Nilsen, J.; Rhee, J.; Zhou, M.; Doetschman, T.; Coffin, J.D.; Wyland, J.J.; Hung, Y.T. Changes in cerebral cortex size are governed by fibroblast growth factor during embryogenesis. *Nat. Neurosci.*, **1999**, *2*(3), 246-253.

[179] Vaccarino, F.M.; Schwartz, M.L.; Raballo, R.; Rhee, J.; Lyn-Cook, R. Fibroblast growth factor signaling regulates growth and morphogenesis at multiple steps during brain development. *Curr. Top. Dev. Biol.*, **1999**, *46*, 179-200.

[180] Molteni, R.; Fumagalli, F.; Magnaghi, V.; Roceri, M.; Gennarelli, M.; Racagni, G.; Melcangi, R.C.; Riva, M.A. Modulation of fibroblast growth factor-2 by stress and corticosteroids: from developmental events to adult brain plasticity. *Brain Res. Brain Res. Rev.*, **2001**, *37*(1-3), 249-258.

[181] Grothe, C.; Wewetzer, K. Fibroblast growth factor and its implications for developing and regenerating neurons. *Int. J. Dev. Biol.*, **1996**, *40*(1), 403-410.

[182] Vicario-Abejon, C.; Johe, K.K.; Hazel, T.G.; Collazo, D.; McKay, R.D. Functions of basic fibroblast growth factor and neurotrophins in the differentiation of hippocampal neurons. *Neuron*, **1995**, *15*(1), 105-114.

[183] Wagner, J.P.; Black, I.B.; DiCicco-Bloom, E. Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor. *J. Neurosci.*, **1999**, *19*(14), 6006-6016.

[184] Gomez-Pinilla, F.; van der Wal, E.A.; Cotman, C.W. Possible coordinated gene expressions for FGF receptor, FGF-5, and FGF-2 following seizures. *Exp. Neurol.*, **1995**, *133*(2), 164-174.

[185] Belcheva, M.M.; Haas, P.D.; Tan, Y.; Heaton, V.M.; Coscia, C.J. The fibroblast growth factor receptor is at the site of convergence between mu-opioid receptor and growth factor signaling pathways in rat C6 glioma cells. *J. Pharmacol. Exp. Ther.*, **2002**, *303*(3), 909-918.

[186] Tsuchioka, M.; Takebayashi, M.; Hisaoka, K.; Maeda, N.; Nakata, Y. Serotonin (5-HT) induces glial cell line-derived neurotrophic factor (GDNF) mRNA expression via the transactivation of fibroblast growth factor receptor 2 (FGFR2) in rat C6 glioma cells. *J. Neurochem.*, **2008**, *106*(1), 244-257.

[187] Asimaki, O.; Leondaritis, G.; Lois, G.; Sakellaridis, N.; Mangoura, D. Cannabinoid 1 receptor-dependent transactivation of fibroblast growth factor receptor 1 emanates from lipid rafts and amplifies extracellular signal-regulated kinase 1/2 activation in embryonic cortical neurons. *J. Neurochem.*, **2011**, *116*(5), 866-873.

[188] Cheng, K.; Zimniak, P.; Raufman, J.P. Transactivation of the epidermal growth factor receptor mediates cholinergic agonist-induced proliferation of H508 human colon cancer cells. *Cancer Res.*, **2003**, *63*(20), 6744-6750.

[189] Keely, S.J.; Uribe, J.M.; Barrett, K.E. Carbachol stimulates transactivation of epidermal growth factor receptor and mitogen-activated protein kinase in T84 cells. Implications for carbachol-stimulated chloride secretion. *J. Biol. Chem.*, **1998**, *273*(42), 27111-27117.

[190] Keely, S.J.; Calandrella, S.O.; Barrett, K.E. Carbachol-stimulated transactivation of epidermal growth factor receptor and mitogen-activated protein kinase in T(84) cells is mediated by intracellular ca(2+), PYK-2, and p60(src). *J. Biol. Chem.*, **2000**, *275*(17), 12619-12625.

[191] McCole, D.F.; Keely, S.J.; Coffey, R.J.; Barrett, K.E. Transactivation of the epidermal growth factor receptor in colonic epithelial cells by carbachol requires extracellular release of transforming growth factor-alpha. *J. Biol. Chem.*, **2002**, *277*(45), 42603-42612.

[192] Park, Y.S.; Cho, N.J. EGFR and PKC are involved in the activation of ERK1/2 and p90 RSK and the subsequent proliferation of SNU-407 colon cancer cells by muscarinic acetylcholine receptors. *Mol. Cell Biochem.*, **2012**, *370*(1-2), 191-198.

[193] Lin, A.L.; Zhu, B.; Zhang, W.; Dang, H.; Zhang, B.X.; Katz, M.S.; Yeh, C.K. Distinct pathways of ERK activation by the muscarinic agonists pilocarpine and carbachol in a human salivary cell line. *Am. J. Physiol Cell Physiol*, **2008**, *294*(6), C1454-C1464.

[194] Krieg, T.; Cui, L.; Qin, Q.; Cohen, M.V.; Downey, J.M. Mitochondrial ROS generation following acetylcholine-induced EGF receptor transactivation requires metalloproteinase cleavage of proHB-EGF. *J. Mol. Cell Cardiol.*, **2004**, *36*(3), 435-443.

[195] Paulmichl, M.; Nasmith, P.; Hellmiss, R.; Reed, K.; Boyle, W.A.; Nerbonne, J.M.; Peralta, E.G.; Clapham, D.E. Cloning and expression of a rat cardiac delayed rectifier potassium channel. *Proc. Natl. Acad. Sci. U. S. A*, **1991**, *88*(17), 7892-7895.

[196] Tsai, W.; Morielli, A.D.; Peralta, E.G. The m1 muscarinic acetylcholine receptor transactivates the EGF receptor to modulate ion channel activity. *EMBO J.*, **1997**, *16*(15), 4597-4605.

[197] Stirnweiss, J.; Valkova, C.; Ziesche, E.; Drube, S.; Liebmann, C. Muscarinic M2 receptors mediate transactivation of EGF receptor through Fyn kinase and without matrix metalloproteases. *Cell Signal.*, **2006**, *18*(8), 1338-1349.

[198] Edelstein, J.; Hao, T.; Cao, Q.; Morales, L.; Rockwell, P. Crosstalk between VEGFR2 and muscarinic receptors regulates the mTOR pathway in serum starved SK-N-SH human neuroblastoma cells. *Cell Signal.*, **2011**, *23*(1), 239-248.

[199] Gomes, E.; Papa, L.; Hao, T.; Rockwell, P. The VEGFR2 and PKA pathways converge at MEK/ERK1/2 to promote survival in serum deprived neuronal cells. *Mol. Cell Biochem.*, **2007**, *305*(1-2), 179-190.

[200] Greenwood, J.M.; Dragunow, M. M3 muscarinic receptors promote cell survival through activation of the extracellular regulated kinase (ERK1/2) pathway. *Eur. J. Pharmacol.*, **2010**, *640*(1-3), 38-45.

[201] Zhou, W.; Zhu, X.; Zhu, L.; Cui, Y.Y.; Wang, H.; Qi, H.; Ren, Q.S.; Chen, H.Z. Neuroprotection of muscarinic receptor agonist pilocarpine against glutamate-induced apoptosis in retinal neurons. *Cell Mol. Neurobiol.*, **2008**, *28*(2), 263-275.

[202] Gomes, E.; Rockwell, P. p38 MAPK as a negative regulator of VEGF/VEGFR2 signaling pathway in serum deprived human SK-N-SH neuroblastoma cells. *Neurosci. Lett.*, **2008**, *431*(2), 95-100.

[203] Autio, H.; Matlik, K.; Rantamaki, T.; Lindemann, L.; Hoener, M.C.; Chao, M.; Arumae, U.; Castren, E. Acetylcholinesterase inhibitors rapidly activate Trk neurotrophin receptors in the mouse hippocampus. *Neuropharmacology*, **2011**, *61*(8), 1291-1296.

[204] Stefano, L.; Rossler, O.G.; Griesemer, D.; Hoth, M.; Thiel, G. P2X(7) receptor stimulation upregulates Egr-1 biosynthesis involving a cytosolic Ca(2+) rise, transactivation of the EGF receptor and phosphorylation of ERK and Elk-1. *J. Cell Physiol*, **2007**, *213*(1), 36-44.

[205] Dziedzic, B.; Prevot, V.; Lomniczi, A.; Jung, H.; Cornea, A.; Ojeda, S.R. Neuron-to-glia signaling mediated by excitatory amino acid receptors regulates ErbB receptor function in astroglial cells of the neuroendocrine brain. *J. Neurosci.*, **2003**, *23*(3), 915-926.

[206] Gage, F.H.; Kempermann, G.; Palmer, T.D.; Peterson, D.A.; Ray, J. Multipotent progenitor cells in the adult dentate gyrus. *J. Neurobiol.*, **1998**, *36*(2), 249-266.

[207] Palmer, T.D.; Markakis, E.A.; Willhoite, A.R.; Safar, F.; Gage, F.H. Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. *J. Neurosci.*, **1999**, *19*(19), 8487-8497.

[208] Vescovi, A.L.; Reynolds, B.A.; Fraser, D.D.; Weiss, S. bFGF regulates the proliferative fate of unipotent (neuronal) and bipotent (neuronal/astroglial) EGF-generated CNS progenitor cells. *Neuron*, **1993**, *11*(5), 951-966.

[209] Gritti, A.; Frolichsthal-Schoeller, P.; Galli, R.; Parati, E.A.; Cova, L.; Pagano, S.F.; Bjornson, C.R.; Vescovi, A.L. Epidermal and fibroblast growth factors behave as mitogenic regulators for a single multipotent stem cell-like population from the subventricular region of the adult mouse forebrain. *J. Neurosci.*, **1999**, *19*(9), 3287-3297.

[210] Jin, K.; Sun, Y.; Xie, L.; Batteur, S.; Mao, X.O.; Smelick, C.; Logvinova, A.; Greenberg, D.A. Neurogenesis and aging: FGF-2 and HB-EGF restore neurogenesis in hippocampus and subventricular zone of aged mice. *Aging Cell*, **2003**, *2*(3), 175-183.

[211] Tao, Y.; Black, I.B.; DiCicco-Bloom, E. *In vivo* neurogenesis is inhibited by neutralizing antibodies to basic fibroblast growth factor. *J. Neurobiol.*, **1997**, *33*(3), 289-296.

[212] Raballo, R.; Rhee, J.; Lyn-Cook, R.; Leckman, J.F.; Schwartz, M.L.; Vaccarino, F.M. Basic fibroblast growth factor (Fgf2) is necessary for cell proliferation and neurogenesis in the developing cerebral cortex. *J. Neurosci.*, **2000**, *20*(13), 5012-5023.

[213] Lie, D.C.; Dziewczapolski, G.; Willhoite, A.R.; Kaspar, B.K.; Shults, C.W.; Gage, F.H. The adult substantia nigra contains progenitor cells with neurogenic potential. *J. Neurosci.*, **2002**, *22*(15), 6639-6649.

[214] Palmer, T.D.; Ray, J.; Gage, F.H. FGF-2-responsive neuronal progenitors reside in proliferative and quiescent regions of the adult rodent brain. *Mol. Cell Neurosci.*, **1995**, *6*(5), 474-486.

[215] Rai, K.S.; Hattiangady, B.; Shetty, A.K. Enhanced production and dendritic growth of new dentate granule cells in the middle-aged hippocampus following intracerebroventricular FGF-2 infusions. *Eur. J. Neurosci.*, **2007**, *26*(7), 1765-1779.

[216] Walicke, P.; Cowan, W.M.; Ueno, N.; Baird, A.; Guillemin, R. Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension. *Proc. Natl. Acad. Sci. U. S. A*, **1986**, *83*(9), 3012-3016.

[217] Aoyagi, A.; Nishikawa, K.; Saito, H.; Abe, K. Characterization of basic fibroblast growth factor-mediated acceleration of axonal branching in cultured rat hippocampal neurons. *Brain Res.*, **1994**, *661*(1-2), 117-126.

[218] Ramirez, J.J.; Finklestein, S.P.; Keller, J.; Abrams, W.; George, M.N.; Parakh, T. Basic fibroblast growth factor enhances axonal sprouting after cortical injury in rats. *Neuroreport*, **1999**, *10*(6), 1201-1204.

[219] Graham, B.M.; Richardson, R. Acute systemic fibroblast growth factor-2 enhances long-term extinction of fear and reduces reinstatement in rats. *Neuropsychopharmacology*, **2009**, *34*(7), 1875-1882.

[220] Johnson, D.E.; Williams, L.T. Structural and functional diversity in the FGF receptor multigene family. *Adv. Cancer Res.*, **1993**, *60*, 1-41.

[221] Turner, C.A.; Akil, H.; Watson, S.J.; Evans, S.J. The fibroblast growth factor system and mood disorders. *Biol. Psychiatry*, **2006**, *59*(12), 1128-1135.

[222] Stauber, D.J.; DiGabriele, A.D.; Hendrickson, W.A. Structural interactions of fibroblast growth factor receptor with its ligands. *Proc. Natl. Acad. Sci. U. S. A*, **2000**, *97*(1), 49-54.

[223] Ibrahimi, O.A.; Zhang, F.; Hrstka, S.C.; Mohammadi, M.; Linhardt, R.J. Kinetic model for FGF, FGFR, and proteoglycan signal transduction complex assembly. *Biochemistry*, **2004**, *43*(16), 4724-4730.

[224] Mohammadi, M.; Dikic, I.; Sorokin, A.; Burgess, W.H.; Jaye, M.; Schlessinger, J. Identification of six novel autophosphorylation sites on fibroblast growth factor receptor 1 and elucidation of their importance in receptor activation and signal transduction. *Mol. Cell Biol.*, **1996**, *16*(3), 977-989.

[225] Wiedlocha, A.; Sorensen, V. Signaling, internalization, and intracellular activity of fibroblast growth factor. *Curr. Top. Microbiol. Immunol.*, **2004**, *286*, 45-79.

[226] Belluardo, N.; Wu, G.; Mudo, G.; Hansson, A.C.; Pettersson, R.; Fuxe, K. Comparative localization of fibroblast growth factor receptor-1, -2, and -3 mRNAs in the rat brain: in situ hybridization analysis. *J. Comp Neurol.*, **1997**, *379*(2), 226-246.

[227] Asai, T.; Wanaka, A.; Kato, H.; Masana, Y.; Seo, M.; Tohyama, M. Differential expression of two members of FGF receptor gene family, FGFR-1 and FGFR-2 mRNA, in the adult rat central nervous system. *Brain Res. Mol. Brain Res.*, **1993**, *17*(1-2), 174-178.

[228] Yazaki, N.; Hosoi, Y.; Kawabata, K.; Miyake, A.; Minami, M.; Satoh, M.; Ohta, M.; Kawasaki, T.; Itoh, N. Differential expression patterns of mRNAs for members of the fibroblast growth factor receptor family, FGFR-1-FGFR-4, in rat brain. *J. Neurosci. Res.*, **1994**, *37*(4), 445-452.

[229] Takami, K.; Matsuo, A.; Terai, K.; Walker, D.G.; McGeer, E.G.; McGeer, P.L. Fibroblast growth factor receptor-1 expression in the cortex and hippocampus in Alzheimer's disease. *Brain Res.*, **1998**, *802*(1-2), 89-97.

[230] Miyake, A.; Hattori, Y.; Ohta, M.; Itoh, N. Rat oligodendrocytes and astrocytes preferentially express fibroblast growth factor receptor-2 and -3 mRNAs. *J. Neurosci. Res.*, **1996**, *45*(5), 534-541.

[231] Fuhrmann, V.; Kinkl, N.; Leveillard, T.; Sahel, J.; Hicks, D. Fibroblast growth factor receptor 4 (FGFR4) is expressed in adult rat and human retinal photoreceptors and neurons. *J. Mol. Neurosci.*, **1999**, *13*(1-2), 187-197.

[232] Belluardo, N.; Blum, M.; Mudo, G.; Andbjer, B.; Fuxe, K. Acute intermittent nicotine treatment produces regional increases of basic fibroblast growth factor messenger RNA and protein in the tel- and diencephalon of the rat. *Neuroscience*, **1998**, *83*(3), 723-740.

[233] Belluardo, N.; Mudo, G.; Caniglia, G.; Cheng, Q.; Blum, M.; Fuxe, K. The nicotinic acetylcholine receptor agonist ABT-594 increases FGF-2 expression in various rat brain regions. *Neuroreport*, **1999**, *10*(18), 3909-3913.

[234] Belluardo, N.; Mudo, G.; Blum, M.; Cheng, Q.; Caniglia, G.; Dell'Albani, P.; Fuxe, K. The nicotinic acetylcholine receptor agonist (+/-)-epibatidine increases FGF-2 mRNA and protein levels in the rat brain. *Brain Res. Mol. Brain Res.*, **1999**, *74*(1-2), 98-110.

[235] Maggio, R.; Riva, M.; Vaglini, F.; Fornai, F.; Racagni, G.; Corsini, G.U. Striatal increase of neurotrophic factors as a mechanism of nicotine protection in experimental parkinsonism. *J. Neural Transm.*, **1997**, *104*(10), 1113-1123.

[236] Son, J.H.; Winzer-Serhan, U.H. Chronic neonatal nicotine exposure increases mRNA expression of neurotrophic factors in the postnatal rat hippocampus. *Brain Res.*, **2009**, *1278*, 1-14.

[237] Belluardo, N.; Mudo', G.; Bonomo, A.; Di, L., V; Frinchi, M.; Fuxe, K. Nicotine-induced fibroblast growth factor-2 restores the age-related decline of precursor cell proliferation in the subventricular zone of rat brain. *Brain Res.*, **2008**, *1193*, 12-24.

[238] Stachowiak, M.K.; Moffett, J.; Joy, A.; Puchacz, E.; Florkiewicz, R.; Stachowiak, E.K. Regulation of bFGF gene expression and subcellular distribution of bFGF protein in adrenal medullary cells. *J. Cell Biol.*, **1994**, *127*(1), 203-223.

[239] Moffett, J.; Kratz, E.; Stachowiak, M.K. Increased tyrosine phosphorylation and novel cis-acting element mediate activation of the fibroblast growth factor-2 (FGF-2) gene by nicotinic acetylcholine receptor. New mechanism for trans-synaptic regulation of cellular development and plasticity. *Brain Res. Mol. Brain Res.*, **1998**, *55*(2), 293-305.

[240] Cucina, A.; Sapienza, P.; Corvino, V.; Borrelli, V.; Mariani, V.; Randone, B.; Santoro, D.L.; Cavallaro, A. Nicotine-induced smooth muscle cell proliferation is mediated through bFGF and TGF-beta 1. *Surgery*, **2000**, *127*(3), 316-322.

[241] Cucina, A.; Corvino, V.; Sapienza, P.; Borrelli, V.; Lucarelli, M.; Scarpa, S.; Strom, R.; Santoro-D'Angelo, L.; Cavallaro, A. Nicotine regulates basic fibroblastic growth factor and transforming growth factor beta1 production in endothelial cells. *Biochem. Biophys. Res. Commun.*, **1999**, *257*(2), 306-312.

[242] Blum, M.; Wu, G.; Mudo, G.; Belluardo, N.; Andersson, K.; Agnati, L.F.; Fuxe, K. Chronic continuous infusion of (-)nicotine reduces basic fibroblast growth factor messenger RNA levels in the ventral midbrain of the intact but not of the 6-hydroxydopamine-lesioned rat. *Neuroscience*, **1996**, *70*(1), 169-177.

[243] Liu, F.L.; Fuxe, K.; Belluardo, N.; Leo, G.; Agnati, L.F.; Aguirre, J.A. Acute intermittent nicotine treatment produces a reduction in the total number of FGF-2 immunoreactive astroglial cells in the substantia nigra of the rat: a stereological analysis. *Neurosci. Lett.*, **2004**, *355*(3), 181-184.

[244] Barathi, V.A.; Weon, S.R.; Beuerman, R.W. Expression of muscarinic receptors in human and mouse sclera and their role in the regulation of scleral fibroblasts proliferation. *Mol. Vis.*, **2009**, *15*, 1277-1293.

[245] Borroto-Escuela, D.O.; Romero-Fernandez, W.; Garriga, P.; Ciruela, F.; Narvaez, M.; Tarakanov, A.O.; Palkovits, M.; Agnati, L.F.; Fuxe, K. G protein-coupled receptor heterodimerization in the brain. *Methods Enzymol.*, **2013**, *521*, 281-294.

**Received: March 04, 2013** **Revised: October 30, 2013** **Accepted: August 13, 2014**